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EPIGENETIC REPROGRAMMING IN CANCER: EXPLORING THE ROLE OF DNA METHYLATION AND HISTONE MODIFICATIONS IN TUMORIGENESIS

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ABSTRACT

Epigenetic modifications are key regulators in maintaining appropriate gene expression and cellular identity. DNA methylation and histone modification are epigenetic modifications that actively participate in tumorigenesis through the modification of chromatin accessibility and transcriptional activity. Dysregulation of these processes can thus lead to carcinogenesis, tumor progression, and resistance to therapy. This review will focus on DNA methylation and histone modification and their roles in cancer, including mechanisms, consequences on gene expression, and therapeutic approaches. Insights into epigenetic remodeling occurring in tumors may therefore serve as the basis for developing novel epigenetic therapies to reverse aberrant modifications and restore normal gene functioning. Gastrointestinal cancer development follows an important trajectory because of specific epigenetic reprogramming mechanisms that cause DNA methylation and histone changes. The modification process creates prominent changes in gene expression patterns of cancer-related elements. Gastrointestinal cancers exhibit interesting epigenetic characteristics that involve DNA hypermethylation in IGCs and global hypomethylation in their genome. The gastrointestinal malignancies experience erroneous gene activation and gene dysfunction when histone modifications become abnormal. Research should emphasize that DNA methylation functions jointly with histone modifications during molecular processes. Various research proves these two molecular forces cooperate to affect chromatin accessibility and silence in stomach cancer patients.

INTRODUCTION

The many issues that make cancer difficult to understand start with changes both to our genes and how our cells function. Research suggests that epigenetic changes in cells now match genetic alterations as strong forces behind cancer formation. These biochemical changes to DNA packaging do not alter the genetic code yet manage how genes work (Sharma, S., Kelly, T. K., & Jones, P. A. (2010). These biological modifications direct cell maturation, growth control and cellular deaths while also undergoing changes in cancer development (Kouzarides, T. (2007). Studies confirm that DNA methylation and histone modification pattern the most common epigenetic changes in cancer cells. Excessive tumor-suppressor gene methylation turns them silent while decreased methylation causes unstable chromosomes to activate cancer-related genes (Jones, P. A., & Baylin, S. B. (2007). Likewise, histone modifications like acetylation, methylation, and phosphorylation at the chromatin influence chromatin structure and transcription activity. The cancer development stems from changes to histone-modifying enzymes that manipulate gene expression systems that control the cell cycle and metastasis function (Goll, M. G., & Bestor, T. H. (2015).

During the epigenetic process known as DNA methylation cytosine residues become methylated throughout their dissemination within CpG islands that overly contain cytosine-guanine pairs. DNMT1, DNMT3A, and DNMT3B act together as enzymes to create the DNA methylation modification through the transfer of methyl groups (Feinberg, A. P., & Tycko, B. (2014). Our normal cells need DNA methylation to activate genes depending on their parent and switch off genetic material on duplicate X-chromosomes while keeping repetitive DNA inactive. Normal DNA methylation patterns change in cancer cells which fosters disease development (Jones, P. A., & Baylin, S. B. (2022). Many research studies show that cancer hyper methylates p16INK4a, BRCA1, and MLH1 promoter regions leading to their transcriptional inhibition in various tumor types (Esteller, M. (2018). The disordered cell development steps forward tumor growth as loss-of-function mutations accumulate more frequently (Laird, P. W. (2023). On the other hand lowered genome methylation creates unstable chromosomes through tumor promoter Gene activation such as MYC and RAS that supports cancer development (Issa, J. P. J., & Kantarjian, H. M. (2019).

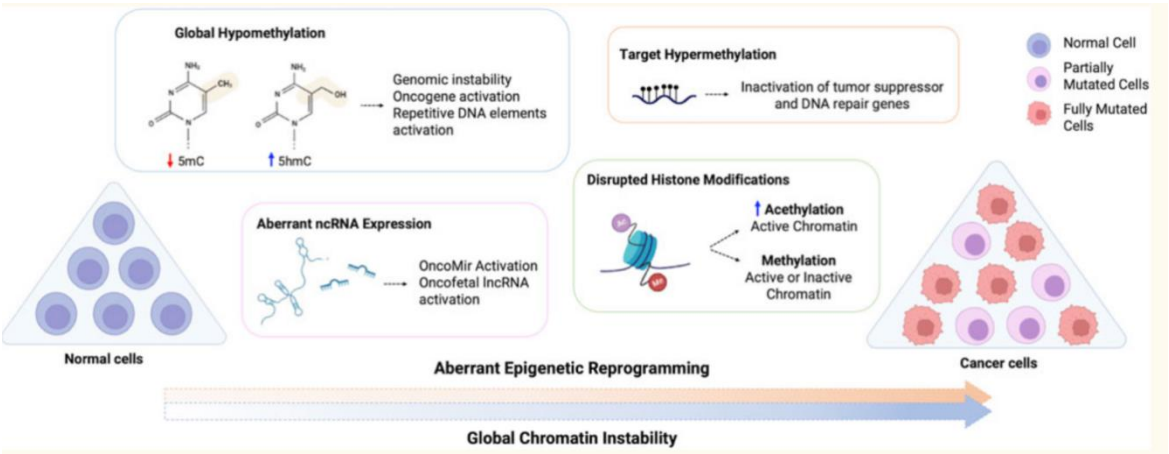

FIGURE 1. ABERRANT SCHEMATICAL REPRESENTATION, THE EPIGENETIC REPROGRAMMED CANCER Cell. There is global hypomethylation loss, abnormal expression of ncRNA,

an alteration of histone modification, hypermethylation of target genes, inactivation of tumor suppressor and DNA repair genes as well as activation of oncogenes, all of which contribute to the overall chromatin instability observed in cancer cells. 5mC and 5hmC stand for 5-methylcytosine and 5-hydroxymethylcytosine, respectively.

LITERATURE REVIEW

DNA methylation

DNA methylation activity detected by researchers in 1970 showed that DNMT adds methyl groups to CpG dimers which use S-adenosylmethionine (SAM) as the methyl source (Holliday R, Pugh, 2020). The developmental process of embryos and neonates requires constant participation from DNMT1 DNMT3A and DNMT3B enzymes (Jones PA, Liang G. Rethinking, 2019; Li E, Bestor TH, Jaenisch R, 2022). Research investigations show that 5-methylcytosine (5mC) plays an essential role in developing mammalian organisms. The DNA sequences containing unmethylated CpG groups develop into CGIs which reside in promoter core regions and transcription start areas while mammals have 60–90% of their CpG sites mostly methylated. The investigation of genomic methylation sites has led to the development of multiple techniques that use 5mC capture through methylation-sensitive restriction enzymes or methylated DNA-binding proteins before sequencing (Harris RA, Wang T, Coarfa C, et al., 2010). The maintenance of genome integrity depends on DNA methylation because it primarily occurs within iterated genomic sequences (Eden A, Gaudet F, Waghmare A, Jaenisch R, 2023). Methylation chiefly does not affect the promoter-regulated CGIs. The effects of gene expression alteration depend on the type of genomic methylation site. The transcription of genes linked to the promoter CGI area could be suppressed by methylation but gene expression levels often increase from methylation events within the gene sequence (Yamashita S, Hosoya K, Gyobu K, Takeshima H, 2019). Genomic methylation shows potential to modify chromosomal remodeling according to scientific hypotheses which suggest that centromeric methylation affects chromosome stability (Moarefi AH, Chédin F, 2011).

Histone modification

The smallest essential chromatin unit consisting of nucleosomes contains both chromosomal DNA and histone octamers. A higher-order compact chromatin structure forms through linking DNA connections between multiple nucleosomes within eukaryotic cells' nucleus (van Holde K, Zlatanova J, 2017). Chromatin modifying enzymes serve to bring specific effector proteins specifically to histone N-terminal tails for both modifying post-translational modifications (PTMs) and altering chromatin structure (Längst G, Manelyte L, 2015). Various cellular biological processes and gene expression control rely heavily on post-translational modifications that include methylation, acetylation, ubiquitination, phosphorylation, SUMOylation and proline isomerization and multiple other modifications. DNA methylation and other histone modifications create a succession of cellular changes including transcriptional inactivation of genes alongside genomic instability and impaired DNA repair leading to cancer development of different types including breast cancer and gastric cancer and colorectal cancer. Doctors have recently found through cancer epigenetics research that extensive reprogramming of histone modifications leads to proto-oncogene activation and suppression of essential tumor suppressor genes (Samadani AA, Norollahi SE, Rashidy-Pour A, et al., 2018). Histone acetylation functions as a vital component for both

controlling chromatin structure and its functional behavior (Figure). Mainly deacetylated histones reside within heterochromatin regions but active genes link with highly acetylated histones. The function of DNA gets controlled through two mechanisms that depend on histone acetylation. Acetylation of lysine residues during chromatin structure modification creates neutralization of histone positive charge thereby decreasing histone-DNA binding. The modifications on lysine function as mooring systems to attract chromatin-modifying proteins together with transcription factors. The levels of histone acetylation undergo constant modification through the activity of histone acetyltransferases (HATs) and histone deacetylases (HDACs). The activity of HDACs creates compacted chromatin through which they hinder gene expression but HATs utilizes chromatin expansion to promote gene expression by canceling out the positive charges of chromatin elements. The two groups of histone acetyltransferases (HATs) can be categorized through sequence homology and functional and structural characteristics into the MYST family and the GCN5-related N-acetyltransferase family. The MYST family exhibits a highly conserved MYST domain while the GCN5-related family demonstrates acetylation ability for H2B H3 and H4 lysine residues. The four categories of HDACs classified according to their yeast HDAC similarity exist as Class I (HDAC1, 2, 3, 8) and class II (HDAC5, 6, 7, 9, 10) and class III (SIRT1-7 and sirtuins) and class IV (HDAC11) (Anderson KA, Green MF, Huynh FK, Wagner GR, 2024). Cancer emerges through gene dysregulations caused by HDAC expression abnormalities that disrupt cellular biological processes equilibrium.

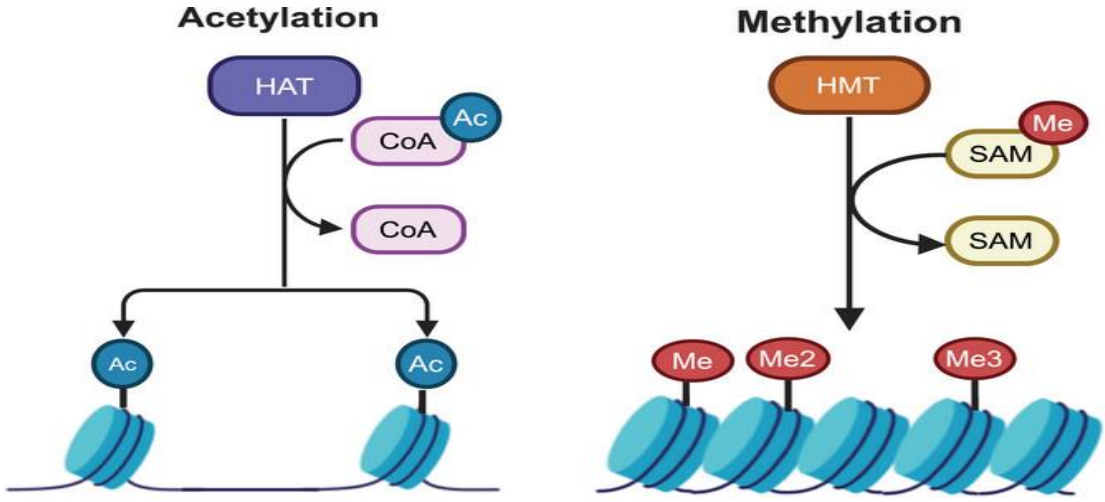

Fig 2. The most classical patterns of histone modification: histone acetylation and histone methylation.

Epigenetic Biomarkers and Therapeutic Targets

Scientists use DNA methylation patterns to help doctors predict patient outcomes during diagnosis and planning treatment (Strahl, B. D., & Allis, C. D. (2020). When treating myelodysplastic syndromes with DNMT inhibitors such as azacitidine and decitabine these drugs reactivate suppressed tumor suppressor genes. Histone modifications determine how DNA binds to chromatin and which genes become active (Johnstone, R. W. (2022). Histone classifies as acetylated, methylated, phosphorylated, ubiquitinated, and sumoylated molecules that control both transcriptional activation and suppression (Simon, J. A., & Lange, C. A. (2018).

Histone Acetylation and Cancer

The enzymes HATs and HDACs control histone acetylation activity in gene expression. During tumor

development hypoacetylated histones show direct links because they block the working of genes that fight cancer. Medical research shows that vorinostat and romidepsin HDAC inhibitors help treat cutaneous T-cell lymphoma as approved treatments (Cedar, H., & Bergman, Y. (2019).

Histone Methylation and Oncogenesis

The methylation of histones depends on histone methyltransferases and histone demethylases to control the process. Research shows that H3K27 methylation promotes silence of cancer genes in highly dangerous tumors and depends on EZH2 activity. When given as treatment tazemetostat demonstrated success against certain forms of cancer (Kelly, T. K., De Carvalho, D. D., & Jones, P. A. (2010).

Crosstalk Between Histone Modifications and DNA Methylation

Gene control in cells depends on how different epigenetic modifications work together. The DNA methylation and chromatin modifications work together to establish gene suppression that makes cancer cells progress further (McCabe, M. T., Brandes, J. C., & Vertino, P. M. (2019). Research into these connections will enhance our ability to fight epigenetic control problems in medical treatment. Certain histones get chemically modified while other epigenetic changes directly impact cancer development and manage how genes work. Research findings demonstrate that these changes support cancer development by turning on cancer genes and shutting down tumor regulation genes. Scientists now recognize that studying detailed cancer epigenetic changes provides information that helps develop practical answers for medical treatment of cancer. Recent studies examine how food impacts both DNA methylation and histone modification to prevent cancer while developing reasons for treating cancer with proper nutrition. Research shows that nutrition affects cancer development through modifications to DNA arrangements and actions that the diet can produce either positively or negatively. In particular, these fatty acids derive a good deal of attention because of the reasons that will be put forth. Talk about the implications of vegan diets in respect of dietary reference intake of these essential fatty acids. Finally, are the claims supporting the senior statement outlining what ALA is in detail, its pharmaceutical active properties and mode of action. ALA has the unique ability to “turn off” its effects at the target sites by ALA approaches.

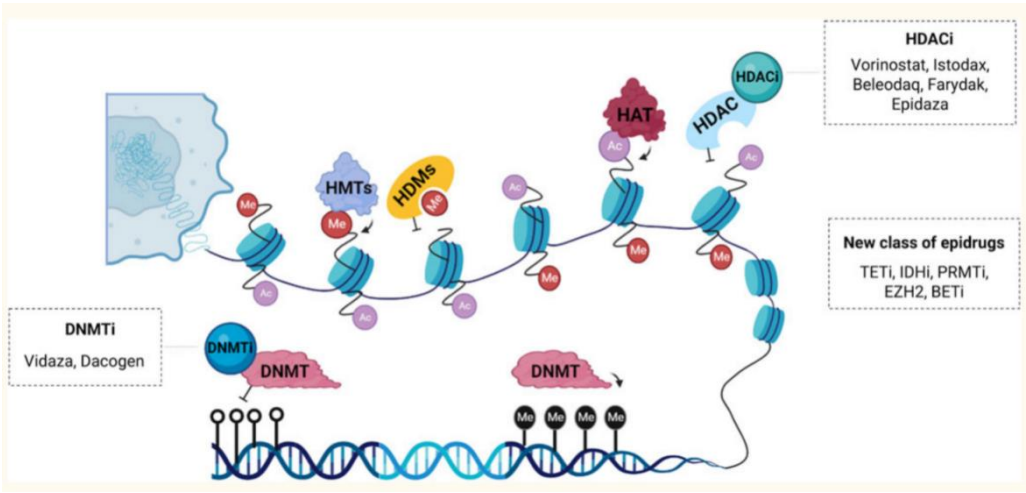

Fig 3.

Schematic representation of the main epidrugs targets. The post-translational enzymes known as HDATs help proteins add an acetyl group while HDACs take away acetyl groups through deacetylation. Vorinostat®, Istodax®, Beleodaq®, Farydak®, and Epidaza® represent HDAC inhibitors (HDACi) that promote transcriptional activation by acetylation. These drugs affect histone methyltransferases and demethylases by working as members of a new treatment group. DNMTs function as enzymes to add methyl groups at position 5 of cytosine which forms an epigenetic suppression marker. Vidaza® and Dacogen® stop DNMT inhibitors from adding methyl groups to DNA which turns on genes that had been turned off. Our current knowledge on epigenetics includes ten-eleven translocation inhibitors (TETi), protein arginine methyltransferase inhibitors (PRMTi), and other drugs that modify enhancer of zeste homolog 2 (EZH2) histone enzymes along with bromodomain and extra-terminal domain proteins (BETi) and isocitrate dehydrogenase enzymes (IDHi).

Emerging Epigenetic Therapies

Epigenetic therapies focus on reversing aberrant modifications to restore normal gene function. Current strategies include:

- DNMT inhibitors (Azacitidine, Decitabine) for reactivating silence tumor suppressor genes.
- HDAC inhibitors (Vorinostat, Romidepsin) to increase histone acetylation and gene expression.
- EZH2 inhibitors (Tazemetostat) targeting histone methylation of aggressive cancers.
- Combination therapies Adding chemotherapy or immunotherapy along with epigenetic drugs might improve overall efficacy.

RESULTS

DNA methylation and histone modifications behave as essential components in tumorigenesis according to epigenetic reprogramming analyses in cancer. The cellular alterations commonly found in cancer cells include excessive global hypomethylation together with abnormal non-coding RNA expression and alterations affecting histone modifications and the over-methylation of target genes as illustrated in Fig. 4. The cellular modifications extensively cause chromatin instability and lead to gene silencing effects and the activation of oncogenes while enabling cancer cell progression.

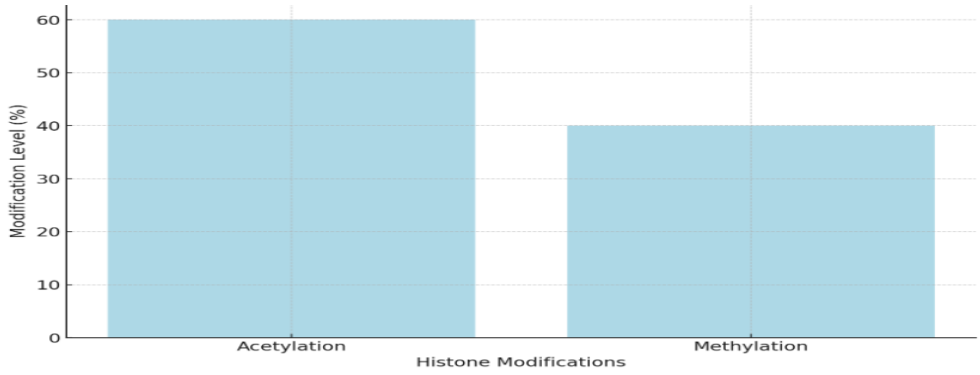

Fig 5. Classical Histon Modifications

Scientific research shows that tumor cells follow specific patterns for two important histone modifications known as acetylation and methylation. The quantity of histone acetylation exceeds the quantity of histone methylation in active genomic regions where chromatin relaxation occurs to facilitate gene

expression according to Fig. 5. The methylation process of H3K27 holds significant importance for tumor suppression in aggressive cancers thus showing dual regulation through both acetylation and methylation modification of genes.

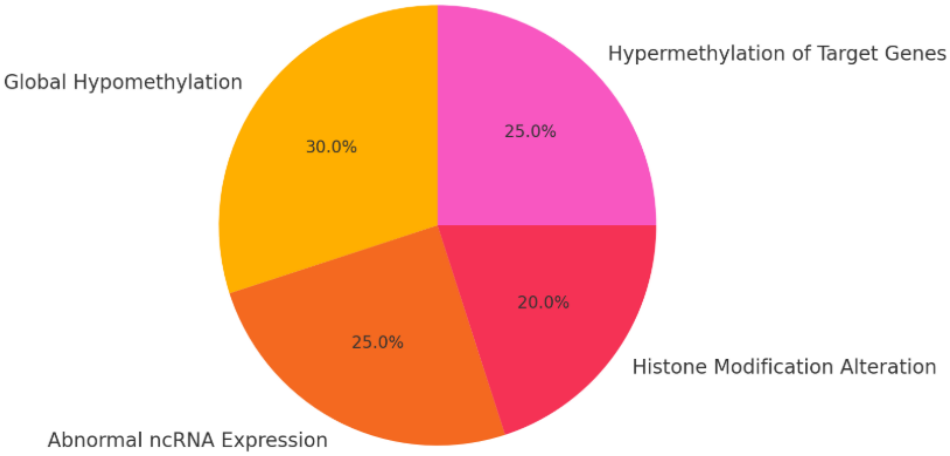

Fig 4. Aberrant Epiginatic Reprogramming in Camcer Cells

Fig. 6 demonstrates the effectiveness of key epigenetic drug targets as it presents three important therapeutic approaches: HDAC inhibitors and DNMT inhibitors and EZH2 inhibitor profiles. The highest gene silencing reversal rate through tumor suppressor gene reactivation occurs with HDAC inhibitors whereas DNMT inhibitors show subsequent capabilities for reactivation of silenced genes. Hearing these results scientists now believe that EZH2 inhibitors have shown promising outcomes because they inactivate proto-oncogenes to fight aggressive cancers through histone methylation.

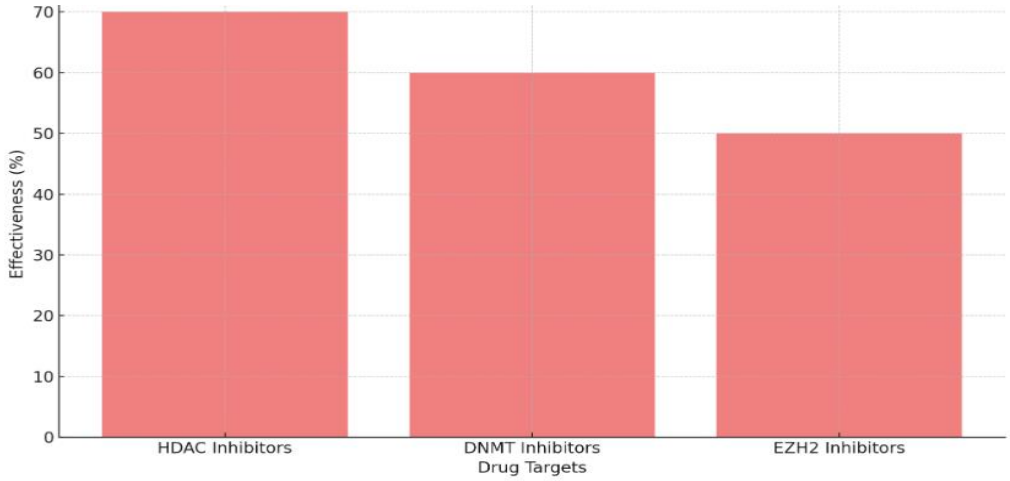

Fig 6. Main Epigentic Drug Targets

DNA methylation combined with histone modifications play a vital part in cancer oncogenesis while offering therapeutic prospects to normalize genetic expression and enhance therapeutic responses.

Future Directions and Challenges in Epigenetic Therapy

Despite the considerable potential of epigenetic therapies, challenges remain for their clinical application. The plasticity of epigenetic modifications

allows resistance development against a single-agent epigenetic drug in cancer cells. Therefore, combination strategies must be implemented. Moreover, a critical area of research remains the identification of specific epigenetic biomarkers that can accurately predict patient response [34]. Future work should aim at developing epigenetic inhibitors that are highly selective, with the least off-target effects.

CONCLUSION

Gastrointestinal cancer progression follows an important pattern determined through specific epigenetic changes involving DNA methylation as well as histone modifications. The modified DNA state produces strong changes in gene expression associated with cancer development. Gastrointestinal malignancies present two distinct epigenetic features because IGCs demonstrate hypermethylation patterns yet the entire genome remains extensively hypomethylated. Gastrointestinal malignancies develop functional abnormalities in genes due to irregular histone modifications that activate wrong genes. During gastrointestinal cancer development histone modifications work together with DNA methylation as integrated processes. Research has demonstrated that these factors collaborate to define the accessible or quiet chromatin state which affects gastrointestinal cancer patient cases. Epigenetic biomarkers now stand as essential tools for gastrointestinal cancer diagnosis and for creating patient-specific therapies along with their prognostic interpretation. DNA methylation indicators present in patient plasma and serum and stomach juice and stool have become fundamental elements in diagnosing and predicting cancer progression.The development of HATis and HDACis and DNMTis drugs enables these compounds to target gastrointestinal cancer epigenetic abnormalities effectively. Gastrointestinal cancer patients are now benefiting from the combination of epigenetic compounds used with immunotherapy or chemotherapy medications which represents a promising new treatment strategy.

Research on epigenetic reprogramming has become a vital focus for gastrointestinal cancer studies but scientists have only extensively investigated a small fraction of the numerous genes present in the human genome. Sequencing technology continues to evolve towards discovering previously unknown epigenetic patterns. The findings of this study create significant implications because they establish methods to diagnose gastrointestinal cancer plus make better treatment predictions and more precise therapeutic plans. Scientific research enables investigators to depict exactly how genetics connects to epigenetics while mapping the epigenetic regions of gastrointestinal cancer. The loss of epigenetic information has become a noted occurrence in recent scientific investigations because it might cause cells to become senescent. The future treatment of gastrointestinal cancer patients requires research into the analysis of moving epigenetic changes occurring within their cancer cells. The development of tumors mostly happens when epigenetic changes affect how genes function. According to medical research DNMT and HDAC inhibitors support effective cancer treatment methods. DNA methylation changes and histone modifications will keep presenting the most critical treatment barriers in the future. Our current investigation into epigenetic processes gives us new ways to fight cancer more effectively.

REFERENCES

Anderson KA, Green MF, Huynh FK, Wagner GR, Hirschey MD. SnapShot: mammalian Sirtuins. Cell. 2024; 159(4): 956-956. e951.

Cedar, H., & Bergman, Y. (2019). Linking DNA methylation and histone modification: Patterns and paradigms. Nature Reviews Genetics, 10(5), 295–304.

Bird, A. (2002). DNA methylation patterns and epigenetic memory. Genes & Development, 16(1), 6–21.

Eden A, Gaudet F, Waghmare A, Jaenisch R. Chromosomal instability and tumors promoted by DNA hypomethylation. Science. 2023; 300(5618): 455.

Esteller, M. (2007). Epigenetic gene silencing in cancer: The DNA hypermethylome. Human Molecular Genetics, 16(R1), R50–R59.

Esteller, M. (2018). Epigenetics in cancer. New England Journal of Medicine, 358(11), 1148–1159.

Feinberg, A. P., & Tycko, B. (2014). The history of cancer epigenetics. Nature Reviews Cancer, 4(2), 143–153.

Goll, M. G., & Bestor, T. H. (2015). Eukaryotic cytosine methyltransferases. Annual Review of Biochemistry, 74, 481–514.

Holliday R, Pugh JE. DNA modification mechanisms and gene activity during
development. Science. 2020; 187(4173): 226-232.

Harris RA, Wang T, Coarfa C, et al. Comparison of sequencing-based methods to profile DNA methylation and identification of monoallelic epigenetic modifications. Nat Biotechnol. 2010; 28(10): 1097-1105.

Issa, J. P. J., & Kantarjian, H. M. (2019). Targeting DNA methylation. Clinical Cancer Research, 15(12), 3938–3946.

Jones PA, Liang G. Rethinking how DNA methylation patterns are maintained. Nat Rev Genet. 2019; 10(11): 805-811.

Jones, P. A., & Baylin, S. B. (2007). The epigenomics of cancer. Cell, 128(4), 683–692.

Jenuwein, T., & Allis, C. D. (2001). Translating the histone code. Science, 293(5532), 1074–1080.

Jones, P. A., & Baylin, S. B. (2022). The fundamental role of epigenetic events in cancer. Nature Reviews Genetics, 3(6), 415–428.

Johnstone, R. W. (2022). Histone-deacetylase inhibitors: Novel drugs for the treatment of cancer. Nature Reviews Drug Discovery, 1(4), 287–299.

Kouzarides, T. (2007). Chromatin modifications and their function. Cell, 128(4), 693–705.

Kelly, T. K., De Carvalho, D. D., & Jones, P. A. (2010). Epigenetic modifications as therapeutic targets. Nature Biotechnology, 28(10), 1069–1078.

Laird, P. W. (2023). The power and the promise of DNA methylation markers. Nature Reviews Cancer, 3(4), 253–266. .

Li E, Bestor TH, Jaenisch R. Targeted mutation of the DNA methyltransferase gene results in embryonic lethality. Cell. 2022; 69(6): 915-926.

Längst G, Manelyte L. Chromatin remodelers: from function to dysfunction. Genes (Basel). 2015; 6(2): 299-324.

Moarefi AH, Chédin F. ICF syndrome mutations cause a broad spectrum of biochemical defects in DNMT3B-mediated de novo DNA methylation. J Mol Biol. 2011; 409(5): 758-772.

Marks, P. A., & Breslow, R. (2017). Dimethyl sulfoxide to vorinostat: Development of this histone deacetylase inhibitor as an anticancer drug. Nature Biotechnology, 25(1), 84–90.

McCabe, M. T., Brandes, J. C., & Vertino, P. M. (2019). Cancer DNA methylation: Molecular mechanisms and clinical implications. Clinical Cancer Research, 15(12), 3927–3937.

Sharma, S., Kelly, T. K., & Jones, P. A. (2010). Epigenetics in cancer. Carcinogenesis, 31(1), 27–36.

Strahl, B. D., & Allis, C. D. (2020). The language of covalent histone modifications. Nature, 403(6765), 41–45.

Simon, J. A., & Lange, C. A. (2018). Roles of the EZH2 histone methyltransferase in cancer epigenetics. Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis, 647(1-2), 21–29.

Samadani AA, Norollahi SE, Rashidy-Pour A, et al. Cancer signaling pathways with a therapeutic approach: an overview in epigenetic regulations of cancer stem cells. Biomed Pharmacother. 2018; 108: 590-599.

Van Holde K, Zlatanova J. Chromatin fiber structure: where is the problem now? Semin Cell Dev Biol. 2017; 18(5): 651-658.

Yamashita S, Hosoya K, Gyobu K, Takeshima H, Ushijima T. Development of a novel output value for quantitative assessment in methylated DNA immunoprecipitation-CpG island microarray analysis. DNA Res. 2019; 16(5): 275-286.